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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,390	09/24/2003	Stephen B. Roscoe	58625US002	3951

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3M INNOVATIVE PROPERTIES COMPANY
PO BOX 33427
ST. PAUL, MN 55133-3427

EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,390	ROSCOE ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Note

Claims examined in this Office Action are claims 1-24.

Claim Rejections - 35 USC § 112

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn due to amendments made by the applicant to the set of claims filed on 17 July 2006.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8, and 10-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz et al [Journal of Pharmaceutical Sciences, 1965, volume 54, pages 591-594] in view of Loftsson et al. [Drug Development and Industrial Pharmacy, 1994, volume 20, pages 1699-1708] in view of Tayar et al. [Journal of Pharmaceutical Science, volume 80, 1991, pages 590-598].

Claims 1-5, 8, and 10-24, state:

1. A method of formulating a pharmaceutical composition comprising:
comparing parameters of at least one pharmaceutical and a plurality of compounds, wherein the parameters comprise at least log(P) and molecular weight;
choosing at least one model compound from the plurality of compounds for each pharmaceutical;
providing at least one model compound-excipient formulation comprising at least one model compound and at least one excipient;
measuring the diffusion of a model compound of at least one model compound-excipient formulation across at least one membrane;
choosing a model compound-excipient formulation based on the measured model compound diffusion; and
combining components comprising the at least one pharmaceutical and the excipient package of the chosen model compound-excipient formulation.

2. A method according to claim 1, wherein the model compound-excipient formulation is saturated in model compound.

3. A method according to claim 1, wherein the parameters further comprise the number of freely rotatable bonds.

4. A method according to claim 1, wherein the parameters further comprise the number of hydrogen bond donors and acceptors.

5. A method according to claim 1, wherein the diffusion is measured utilizing a Franz cell.

8. A method according to claim 6, wherein the diffusion of the model compound is simultaneously measured in a plurality of diffusion cells.

10. A method according to claim 1, wherein at least one model compound-excipient formulation comprises a plurality of different excipients.

11. A method according to claim 1, wherein diffusion is measured utilizing a chemical reaction.

12. A method according to claim 1, wherein at least one membrane comprises a synthetic polymer membrane.

13. A method according to claim 1, wherein at least one membrane comprises skin.

14. A method according to claim 1, wherein at least one membrane is selected from the group consisting of hairless mouse skin, snake skin, pig skin, and cadaver skin.

15. A method according to claim 1, wherein the parameters consist of log(P) and molecular weight.

16. A method according to claim 1, wherein at least one parameter of at least one model compound is calculated.

17. A method according to claim 1, wherein at least one parameter of at least one model compound is experimentally determined.

18. A method according to claim 1, wherein at least one parameter of the pharmaceutical is calculated.

19. A method according to claim 1, wherein at least one parameter of the pharmaceutical is experimentally determined.

20. A method according to claim 1, further comprising: contacting the pharmaceutical composition with the skin of a live mammal; and observing the result.

21. A method according to claim 1, further comprising incorporating the pharmaceutical composition into a transdermal delivery system.

22. A method according to claim 21, further comprising contacting the pharmaceutical composition with the skin of a live mammal and observing the result.

23. A method according to claim 21, wherein the transdermal delivery device comprises an adhesive patch.

24. A method according to claim 1, wherein prior to measuring diffusion of each model compound-excipient formulation, it is incorporated into an adhesive patch.

Katz et al. teach aspects of the claimed invention Table 1 (page 593). Table 1 lists molecular weights and partition coefficients for a plurality of molecules. The molecular weights are deduced from the columns listing the combination of weight by volume concentrations and the molar concentrations. The partition coefficients are listed in the fifth column of data.

The McKenzie parameter (p McK-S_{50}) is calculated in the last column as the negative logarithm of dilution producing vasoconstriction of 50% of subjects (Claim 16) while the partition coefficients are experimentally measured (claim 17).

On page 592, column 2, lines 7-11, Katz et al state, "McKenzie and Stoughton... prepared dilutions of the corticosteroids in tenfold dilutions ranging from 1:100 to 1:10,000,000; 0.02 ml of these dilutions were applied to 1-in. areas of the forearm and covered with Saran wrap." The requirements of skin of a live mammal are met. The Saran wrap comprises an adhesive patch, and the chemical is in contact with the adhesive patch (the Saran wrap) before it penetrates the skin. This entire system comprises a transdermal delivery system.

There are two aspects of this rejection that Katz et al. fail to teach:

First, Katz et al. do not teach the compound-excipient formulation, the diffusion method and analysis, saturation of the model compound, impact of rotatable and hydrogen bond donors and acceptors, use of a Franz cell(s), a plurality of excipients, utilization of a chemical reaction, use of a synthetic polymer membrane, calculated and empirical parameters of the pharmaceutical, and a transdermal delivery system.

In addition, while Katz et al. teach a partition coefficient between ether and water, they do not teach the required partition between octanol and water (log (P) is based on the partition coefficient between octanol and water).

To address the second concern, Tayar et al. teach the solvation of 121 solutes in five different solvent systems (octanol-water, heptane-water, chloroform-water, diethyl ether-water, and butyl acetate-water) to tune for a desired comparison of aqueous solvability to lipophilicities [abstract, page 590 and last paragraph, column 2 page 290].

To address the first concern, Loftsson et al. teach a method of making a pharmaceutical composition between hydrocortisone and different cyclodextrins to enhance transdermal delivery. (One of the model compounds listed in Table 1 of Katz et al. is hydrocortisone). Figure 2 of Loftsson et al. teaches a relationship between diffusion through a membrane and cortisone concentration as the combination of the hydrocortisone and each of the cyclodextrins used in the formulation. Figure 2 additionally uses a synthetic polymer membrane (cellophane).

On page 1705 in Loftsson et al. under "Table 1," shows as excess of cyclodextrin concentration used to saturate the hydrocortisone.

Page 1700 of Loftsson et al., lines 21-24, states, "The molar substitution (MS) i.e. the average number of propylene oxide molecules that have reacted with one glucopyranose unit, was 0.6 or 0.9. HPβCD has a very good aqueous solubility (over 60% w/v) and forms stable complexes with many drugs." The type of molar substitution chosen for the cyclodextrin affects its size, number of rotatable bonds, and hydrogen bonding characteristics.

In Loftsson et al. on page 1702, the sixth and seventh lines from the bottom of the page state, "Female hairless mice were killed by cervical dislocation, their full-thickness skins removed and placed in the previously described Franz diffusion cells." Thus Franz diffusion cells are used to measure diffusion across hairless mouse skin.

Loftsson et al. teach that the chemical reaction between the cyclodextrin and the hydrocortisone is used to affect the diffusion across the skin.

Loftsson et al. teach that the formulation is chosen from one of two different cyclodextrins employed throughout the study.

In Table 2 of Loftsson et al., the standard deviation of the flux needs to be calculated while the flux is.an experimentally measured property.

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine the general corticosteroid study of Katz et al. with the cyclodextrin study of Loftsson et al. and the partition study of Tayar et al. because both Katz and Loftsson investigate cortisones as drugs with the added advantage of Loftsson having the feature of cyclodextrins to enhance drug performance; Tayar is a variation on the type of partition coefficient measured in Katz. It would be obvious to adjust the partition study of Katz et al. from water-ether to water-octanol according to the procedures of this study of Tayar et al. for a desired comparison of aqueous solvability with lipophilicities.

Claims 1 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz in view of Loftsson in view of Tayar as applied to claims 1-5, 8, and 10-24

above, and further in view of Garcia-Ochoa [Chemistry- A European Journal, 1999, volume 5, pp. 897-901].

Claims 6 and 7 claim the drug formulation method of claim 1, wherein at least one model compound comprises a dye and the diffusion is monitored using fluorescence spectroscopy.

Katz, Loftsson, and Tayar claim the drug formulation process as stated in the instant application, but fail to disclose any use of fluorescence or fluorescence spectroscopy.

The last sentence in the second paragraph of the methods on page 901 of Garcia-Ochoa states, "^{1}H NMR spectra of 10^{-3}M solutions of HPMO [a fluorescent dye] in D_2O in the absence and presence of 10^{-2}M β-CD [cyclodextrin] (almost saturated solution) were recorded at 500 MHz on a Varian Unity spectrometer at 303K..." The use of fluorescence and fluorescent spectroscopy is employed to detect the cyclodextrins.

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz in view of Loftsson in view of Tayar as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa, for Garcia-Ochoa is an extension of the cyclodextrin study with the use of fluorescence to more effective monitor cyclodextrin concentration and location.

Claims 1 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz in view of Loftsson in view of Tayar in view of Garcia-Ochoa as applied to

claims 1 and 6-7 above, and further in view of Colarusso et al [Biophysical Journal; February 2002; volume 82, pages 752-761].

Claim 9 claims the method of formulating a pharmaceutical composition of claim 1, but adds the limitation of recording an image of diffusion of a model compound. Claim 8 claims the use of a plurality of diffusion cells.

Katz, Loftsson, Tayar, and Garcia-Ochoa teach of method of formulating a drug using a cortisone and a cyclodextrine and fluorescence, but fail to record any images in their studies.

Colarusso et al. illustrates several fluorescent images of cells and the effects of cyclodextrins on them in Figures 1-4 and 6-7.

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz in view of Loftsson in view of Tayar in view of Garcia-Ochoa as applied to claims 1 and 6-7 above, and further in view of Colarusso et al; Colarusso et al. use cyclodextrins in analyzing images of cells.

Response to Arguments

Applicant's arguments filed 24 April 2006 have been fully considered but they are not persuasive.

On pages 6 to 11 of the "Remarks" of 24 April 2006, applicant reiterates each grounds of obviousness type prior art rejections. The arguments of the applicants rest on the assumption that the pharmaceutical and model compound are distinct and different entities. As stated on page 9 of the Remarks of 24 April 2006, "Applicants

submit that none of the references teaches or properly suggests at least choosing at least one model compound and using the model compound(s) to measure diffusion properties across at least one membrane, much less choosing a model compound-excipient formulation based on the measured model compound diffusion; and combining components comprising the at least one pharmaceutical and the excipient package of the chosen model compound-excipient formulation as is present in claim 1. In this regard, Applicants wish to point out that the model compound is not the actual pharmaceutical itself, but rather a model compound for the pharmaceutical."

Pharmaceutical is defined in the specification on page 2, lines 10-13 as, "any compound that has at least one therapeutic, disease preventive, diagnostic, or prophylactic effect when administered to an animal and/or a human."

The term model compounds is defined on page 5, lines 23-24 as, "Compounds that may be used as model compounds include any known or predicted compounds."

The term excipients are described on page 7 lines 17-18 as, "Excipients are compounds that serve to assist or retard the diffusion of the pharmaceutical across a membrane."

Consequently, there is no limitation requiring a model compound and a pharmaceutical to not both be pharmaceuticals. In addition, there is no definition or limitation in the specification requiring the pharmaceutical and the model compound to not be identical chemical entities. It is interpreted in this Office action that both the pharmaceutical and the model compound are cortisones while the excipient is the cyclodextrin.

The diffusion of the model compound (hydrocortisone) and the model compound excipient combination (cyclodextrin enclosing the hydrocortisone) is illustrated in Figure 2 of Loftsson et al (as described in page 6 of the Office action of 28 November 2005). The particular excipient cyclodextrin (HPβCD) was chosen because it has good aqueous solubility and can form stable complexes with drugs (such as hydrocortisone) [see last paragraph of page 1700 of Loftsson et al]. As is stated in the second sentence of the last paragraph of Loftsson on page 1700, "It is thought that in aqueous topical drug formulations HPβCD keeps lipophilic water-insoluble drug molecules in solution and delivers them to the skin surface where they partition into the skin barrier." Hydrocortisone is both the model compound and pharmaceutical which is combined with the desired cyclodextrin for effective diffusivity across the membrane. The cyclodextrin is chosen as the excipient because it increases the slow diffusivity of the cortisone.

The arguments to the other obviousness type prior art rejections on pages 10-11 of the Remarks of 24 April 2006 rest on the same arguments held for the initial obviousness rejection. These arguments, while considered, do not overcome the previous prior art rejections.

With the definitions of the applicant of these key concepts clarified, the previous prior art rejections still hold.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Andrew Wang, Supervisory Patent Examiner, can be reached at (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Yolanda Chadwick, whose telephone number is (571) 272-0514.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN
29 September 2006

29 September 2006

29 September 2006

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER